REMARKS

Claims 1-6, 8, 15-17, 87-88 and 90-92 are pending.

Claims 9-11, 18-86, and 89 are cancelled without prejudice.

Claims 1 and 87 are amended. Support for the amendment to claim 1 is found in the application as originally filed, specifically in Fig. 1 (by reference to "reversible-crosslink, blunt DNA and late to unidirectional linkers and LM-PCR"); page 16, line 26, page 63, lines 11-16. The labeling method recited in the claims is found on page 70 second last line to page 76, end of page, for example. Blunting is specifically described on page last line, ligation of adaptors is specifically described on page 73, line 1, and amplification using primers that ligate to the adaptors is specifically described on page at the end of page 73, line 9, for example. Labeling is specifically described on page 74, and on page 15, lines 16-18; page 17, lines 6-8; and page 17, line 29-page 18, line 1, for example.

No new matter is added.

Interview Summary

Examiner Fredman is thanked for the interview with the Applicants' representative James S. Keddie on May 8, 2007.

All current rejections were discussed.

Exr. Fredman agreed that amending the claims to recite a "second sample" rather than a "control sample" would likely resolve the new matter rejection.

Rejection of claims under 35 U.S.C. § 112 (written description)

Claims 1-6, 8, 15-17, 87, 88 and 90-92 are rejected under 35 U.S.C. § 112, first paragraph, as containing new matter.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 1 is amended to recite a "second sample", support for which is found in Fig. 1.

It is believed that this rejection is now moot and should be withdrawn. Withdrawal of this rejection is respectfully requested.

Rejection of claims under 35 U.S.C. § 103 – Orlando in view of Schena

Claims 1-6, 8, 15-17, 87, 88 and 90-92 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Orlando (Methods 1997 11:205-214) in view of Schena (Tibtech (1998) 16:301-306).

In an attempt to establish this rejection, the Examiner argues that Orlando's immunoprecipitation-based methods, in combination with Schena's array, render the instant claims unpatentable. This rejection is respectfully traversed.

In summary, the Applicants submit that: a) the rejected claims recite elements that are neither taught nor suggested by the combination of Orlando and Schena; b) the rejected claims recite a genome amplification method that provides unexpected results; and c) the combination of Orlando and Schena provides a method that is quite different to that being claimed. As such, the Applicants believe that this rejection should be withdrawn. To the extent that further discussion is deemed necessary, the Examiner is respectfully referred to the below.

The rejected claims recite the use of an array containing sequences that detect intergenic regions. Further, the rejected claims recite a method in which a non-immunoprecipitated portion of a sample is labeled to produce a second sample. Results obtained using the non-immunoprecipitated sample are compared to results obtained from an immunoprecipitated sample to indicate the region of the genome in the cell to which a protein of interest binds. Also, the rejected claims require that the immunoprecipitated sample and the non-immunoprecipitated sample are amplified by a particular method that includes blunting, ligating adaptors and amplifying using primers that bind to the adaptors.

The differences between the claimed method and Orlando's method are numerous and include, *inter alia*: a) the use of a microarray of intergenic regions, rather than a southern blot of size-separated fragmented genomic DNA, b) a comparison to results obtained using a non-immunoprecipitated sample; c) use of an amplification method that includes blunting sonicated genomic DNA, ligating adaptors and amplifying using primers that bind to the adaptors; and d) dual labeling (i.e., labeling samples with a first and second label).

Schena is cited to fill the gap between Orlando's deficiencies. However, when Schena and Orlando are combined, the fails to provide all of the elements of the claims.

For example, neither Orlando nor Schena mentions a microarray of intergenic regions, a required element of the rejected claims.

In addition, neither Orlando nor Schena mentions a comparison to results obtained using a non-immunoprecipitated sample (i.e., the "second sample") as required by the rejected claims. With this in mind, the Applicants note that Orlando reports that his method produces significant background (see, e.g., page 213 col. 1, lines 6-10 and page 214, col. 1 lines 20-23), which could, in theory, have been reduced by comparison with a non-immunoprecipitated sample. Orlando carefully considered his options to reduce background on page 213, col. 1, lines 12-19 and page 214, col. 1, lines 23-24, and instead of using a non-immunoprecipitated sample (as recited by the rejected claims), he proposed to use nucleic acid sequences that are known to not interact with the protein under study (page 213, col. 1, lines 12-15), DNA obtained from control immunoprecipitations (page 213, col. 1, 15-19), sequences to which the protein is known or suspected to bind (page 214, col. 1, lines 21-23) and "nonspecific sequences" (page 214, col. 1, lines 23-24). None of Orlando's solutions include a comparison to a non-immunoprecipitated sample, as required by the rejected claims.

Since Orlando appears to have put some thought into solving the problem with background and has suggested four solutions, none of which involves the use of a non-immunoprecipitated sample, it is believed that the use of a non-immunoprecipitated sample is a non-obvious solution to the background problems described in Orlando's paper. This solution is not presented by Schena and, as such, it is believed that the rejected claims are patentable over the combination of Orlando and Schena.

Further, neither Orlando nor Schena mentions an amplification method that includes amplification method that includes blunting sonicated DNA, ligating adaptors and amplifying using primers that bind to the adaptors, as required by the rejected claims. As described by Orlando in the paragraph bridging pages 210 and 211, Orlando's methods require digestion of immunoprecipitated DNA with a *restriction enzyme*, ligation of the digested DNA to an adaptor, and amplifying using

primers that bind to the adaptor. Orlando's restriction enzyme-based amplification method introduces significant bias into the labeled sample because restriction enzyme sites are not evenly distributed in a genome. This bias is noted by Orlando on page 211, col. 1, lines 4-14. Again, Orlando appears to have thought about this limitation of his method, and suggests cutting the immunoprecipitated DNA with a variety of restriction enzymes (see page 211, col. 1, lines 12-14). Orlando's suggestion would direct one of skill in the art *away from*, rather than towards, the amplification method that is recited in the claims.

With the above in mind, the Applicants also submit that the amplification method recited in the claims provides unexpected results in that the amplification is unexpectedly reproducible amplification of an entire genome (see, e.g., page 18, lines 17-21, page 82, middle paragraph, and Fig. 5B, which shows that when genomic DNA amplified is using the claim recited method and hybridized to an array of probes, 99.8% of probes on the array produced signals that were essentially identical within the error range). Such reproducible amplification of an entire genome is in stark contrast to restriction enzyme-based amplification methods, which, as discussed in Tanabe[1] (see page 175, col. 1, lines Genes, Chromosomes and Cancer 2003 38: 168-176; paper cited in accompanying IDS), captures as little as 12% of a genome.

The success of the claim-recited amplification method was quite unexpected and could not have been predicted by the prior art (which essentially disclose restriction enzyme-based methods that inherently amplify as little as 12% of a genome).

While the Applicants believe that a declaration should be unnecessary given the above, the Applicants submit a Declaration under 37 C.F.R. § 1.132 by Dr. John Wyrick (the "Wyrick declaration"), the first named inventor in this application. In his declaration, Dr. Wyrick confirms that success of the claim-recited amplification method was quite unexpected.

Finally, the Applicants note that the disclosures of Orlando and Schena, combined in the manner proposed in this Office Action, would result in a method in

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[1] Tanabe is a post-filing paper that discusses problems that are inherent to restriction enzyme-based genome amplification methods.

which transcription factor binding is compared between two distinct samples. This is *not* the method being claimed and, as such, this rejection should be withdrawn.

The Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

Rejection of claims under 35 U.S.C. § 103 – Mercola in view of Schena

Claims 1-6, 8-11, 15-17, 87, 88 and 90-92 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mercola (USPN 6,410,233) in view of Hacia (Nucleic Acids Research (1998) 26(16):3865-3866) and Schena.

In an attempt to establish this rejection, the Examiner argues that Mercola's immunoprecipitation-based methods, in combination with Shena's array and Hacia's dual color labeling system, render the instant claims unpatentable. This rejection is respectfully traversed.

The rejected claims recite the use of an array containing sequences that detect intergenic regions. Further, the rejected claims recite a method in which a second portion of a sample is labeled and used for comparison.

The disclosures of Mercola, Schena and Hacia are completely void of any explicit discussion of arrays that contain sequences that detect intergenic regions. The passage to which the Examiner refers as teaching such arrays (in Mercola: col. 14, lines 48-50) does not teach such arrays. Instead, this passage refers to the immunoprecipitated fragment. As such, the Applicants argument stands firm.

Likewise, the disclosures of Mercola, Schena and Hacia do not explicitly mention any method in which a non-immunoprecipitated portion of a sample is labeled. As such, the references cited in this rejection, taken independently or in any combination, fail to disclose or reasonably suggest each and every element of the rejected claims. With this in mind, the Applicants submit that Orlando's mis-guidance as to which controls to use to reduce background (as discussed in the previous section of this response) indicates that the differences between the claimed method and prior art methods were not obvious.

Further, the Applicants submit that neither Mercola, Schena nor Hacia explicitly disclose the claim recited amplification method, which method provides unexpected results.

Finally, the Applicants further note that the disclosures of Mercola, Schena and Hacia, combined in the manner proposed in this Office Action, would result in a method in which transcription factor binding is compared between two distinct samples. This is *not* the method being claimed and, as such, this rejection should be withdrawn.

The Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

One of Skill in the Art

For the record, the Applicants disagree with the Examiner that one of skill in the art in the field in which chromatin immunoprecipitation assays has at least a Ph.D. with several years of experience. Drs. Schena and Mercola are "experts" in the field, rather than persons of ordinary skill.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone John Brady at (408) 553-3584.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10050560-1.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 15, 2007

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